ClinicalEvidence

Bronchitis (acute)

Search date May 2015

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ABSTRACT

INTRODUCTION: Acute bronchitis affects more than 40 in 1000 adults per year in the UK. The causes are usually considered to be infective, but only around half of people have identifiable pathogens. The role of smoking or of environmental tobacco smoke inhalation in predisposing to acute bronchitis is unclear. One third of people may have longer-term symptoms or recurrence. METHODS AND OUTCOMES: We conducted a systematic review, aiming to answer the following clinical question: What are the effects of treatments for acute bronchitis in people without chronic respiratory disease? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2015 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 420 studies. After deduplication and removal of conference abstracts, 306 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 245 studies and the further review of 61 full publications. Of the 61 full articles evaluated, three updated systematic reviews and three RCTs were added at this update. We performed a GRADE evaluation for 12 PICO combinations. CONCLUSIONS: In this systematic review we categorised the efficacy for six intervention-comparison combinations, based on information about the effectiveness and safety of the following interventions: antibiotics, antihistamines, antitussives, beta2 agonists (inhaled), and expectorants/mucolytics.

QUESTIONS

INTERVENTIONS

TREATMENTS

Covered elsewhere in Clinical Evidence

Asthma in adults (acute)

Asthma in adults (chronic)

Asthma and other wheezing disorders of childhood

Chronic obstructive pulmonary disease

Upper respiratory tract infection

Key points

- Acute bronchitis affects more than 40 in 1000 adults per year in the UK.

  The causes are usually considered to be infective, but only around half of people have identifiable pathogens.

  The role of smoking or environmental tobacco smoke inhalation in predisposing to acute bronchitis is unclear.

  One third of people may have longer-term symptoms or recurrence.
- We searched for evidence of effectiveness from RCTs and systematic reviews of RCTs.
- Antibiotics may have a modest effect on improving cough and other clinical signs of acute bronchitis compared with placebo, but they also increase the risks of adverse effects.
- There remain concerns that widespread use of antimicrobials will lead to resistance.
- We don't know how different antibiotic regimens compare with each another, as we found insufficient evidence from RCTs.

  One review found that azithromycin (a macrolide) may be more effective than amoxicillin or amoxicillin plus clavulanic acid (co-amoxiclav) at reducing clinical failure in people with acute bronchitis. However, this analysis included two open-label studies and evidence was weak.

  We don't know whether smokers without lung disease are more likely to benefit from antibiotics than non-smokers.
- We don't know whether antihistamines, antitussives, inhaled beta$_2$ agonists, or expectorants and mucolytics improve symptoms of acute bronchitis compared with placebo, as we found few good-quality RCTs.

Clinical context

GENERAL BACKGROUND

Acute bronchitis is a common, though usually self-limiting, illness affecting people of all ages. It is also a common reason for presentation to primary care.

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FOCUS OF THE REVIEW

This systematic overview was performed to assess what interventions were suitable to improve outcomes for acute bronchitis, with minimal adverse effects.

COMMENTS ON EVIDENCE

Interventions that assessed the effectiveness of antibiotics had the most evidence, with RCTs judged to be from moderate to low quality. RCTs that assessed antihistamines, antitussive agents, inhaled beta$_2$ agonists, and mucolytics were all judged to be of low to very low quality in terms of their evidence, and clinical conclusions could not be made.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, March 2010, to May 2015. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 420 studies. After deduplication and removal of conference abstracts, 306 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 245 studies and the further review of 61 full publications. Of the 61 full articles evaluated, three updated systematic reviews and three RCTs were added at this update.

DEFINITION

Acute bronchitis is a transient inflammation of the trachea and major bronchi. Clinically, it is diagnosed on the basis of cough and occasionally sputum, dyspnoea, and wheeze. This overview is limited to episodes of acute bronchitis in people (smokers and non-smokers) with no pre-existing respiratory disease (such as a pre-existing diagnosis of asthma or chronic bronchitis, evidence of fixed airflow obstruction, or both) and excluding those with clinical or radiographic evidence of pneumonia. However, the reliance on a clinical definition for acute bronchitis implies that people with conditions such as transient/mild asthma or mild COPD may have been recruited in some of the reported studies.

INCIDENCE/ PREVALENCE

Acute bronchitis affects around 44 in 1000 adults (age over 16 years) per year in the UK, with around 82% of episodes occurring in autumn or winter. [1] One survey found that acute bronchitis was the fifth most common reason for people of any age to present to a general practitioner in Australia. [2]

AETIOLOGY/ RISK FACTORS

Infection is believed to be the trigger for acute bronchitis. However, pathogens have been identified in less than 55% of people. [1] Community studies that attempted to isolate pathogens from the sputum of people with acute bronchitis found viruses in 8% to 23% of people, typical bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*) in 45%, and atypical bacteria (*Mycobacterium pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis*) in 0% to 25%, but their presence did not predict outcomes. [1] [3] [4] It is unclear whether smoking affects the risk for developing acute bronchitis.

PROGNOSIS

Acute bronchitis is regarded as a mild, self-limiting illness, but there are limited data on prognosis and rates of complications, such as chronic cough or progression to chronic bronchitis or pneumonia. One prospective longitudinal study reviewed 653 previously well adults who presented to suburban general practices over a 12-month period with symptoms of acute lower respiratory tract infection. [1] It found that, within the first month of the illness, 20% of people re-presented to their general practitioner with persistent or recurrent symptoms, mostly persistent cough. One RCT of 212 people (in which around 16% took antibiotics outside of the study protocol) found that participants in the no-treatment control group had at least a slight problem with cough for a mean of 11.4 days, with 'moderately bad' cough lasting for a mean of 5.7 days. A large RCT of 2061 adults (aged over 18 years) who presented with acute cough (up to 28 days' duration) or were likely to have a lower respiratory tract infection (excluding clinical pneumonia), but including participants with asthma or COPD (15%), was informative as to the short-term natural history of acute bronchitis. [5] They found that 356/2027 (18%) had a deterioration in illness, the majority with re-consultation due to worsened symptoms. Only three people were hospitalised (2 in the placebo arm, 1 in the antibiotic arm) with a cardiac or respiratory disease within the month. This demonstrates that serious complications are rare in this group, with the sample size unable to determine if comorbidities (heart disease, lung disease, or diabetes), smoking status, or the presence of green sputum would predict worsened outcomes. Another prospective study of 138 previously well adults found that 34% had symptoms consistent with either chronic bronchitis or asthma 3 years after initial presentation with acute bronchitis. [6] It is also unclear whether acute bronchitis plays a causal role in the progression to chronic bronchitis, or is simply a marker of predisposition to chronic lung disease. Although smoking has been identified as the most important risk factor for chronic bronchitis, [7] [8] it is unclear whether the inflammatory effects of cigarette smoke and infection causing acute bronchitis have

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additive effects in leading to chronic inflammatory airway changes. In children, exposure to parental environmental tobacco smoke is associated with an increase in risk for community lower respiratory tract infection in children aged 0 to 2 years, and an increase in symptoms of cough and phlegm in those aged 5 to 16 years. [9]

AIMS OF INTERVENTION

To improve symptoms associated with acute bronchitis; to reduce complications, with minimal adverse effects.

OUTCOMES

Symptom severity (duration of symptoms, particularly cough, sputum production, and fever; limitation of activities; days feeling ill; clinical improvement; clinical cure); **complications of acute bronchitis**, especially chronic cough, pneumonia, and chronic bronchitis; **quality of life**; **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date May 2015. Databases used to identify studies for this systematic overview include: Medline 1966 to May 2015, Embase 1980 to May 2015, The Cochrane Database of Systematic Reviews 2015, issue 5 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and double-blinded RCTs published in English, containing more than 20 people. We excluded all studies described as 'open', 'open label', not blinded, or single-blinded. There was no minimum length of follow-up and studies were not excluded based on loss to follow-up, but people had to receive a minimum of 3 days of treatment. We included people of any age or sex with acute bronchitis. We excluded trials conducted in those who had chronic respiratory disease or other acute respiratory diseases. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributor. In consultation with the expert contributor, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' sections (see below). **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following options, analgesics and oral beta2 agonists, from this overview. **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 28). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

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QUESTION **What are the effects of treatments for acute bronchitis in people without chronic respiratory disease?**

OPTION **ANTIBIOTICS VERSUS PLACEBO AND OTHER NON-ANTIBIOTIC TREATMENTS**

- For GRADE evaluation of interventions for Bronchitis (acute), see table, p 28 .
- Antibiotics have, at best, a modest effect on improving cough and other clinical signs of acute bronchitis compared with placebo, and they are associated with adverse effects.
- There remain concerns that widespread use of antimicrobials will lead to resistance.
- There is no evidence that current smokers without lung disease are more likely to benefit from antibiotics than non-smokers.

Benefits and harms

Antibiotics versus placebo:

We found one systematic review (search date 2014), [10] which identified 17 RCTs in people with acute bronchitis, including smokers but excluding people with chronic bronchitis. Acute bronchitis was defined by a clinical syndrome of cough with or without sputum production, with a physician's diagnosis of acute bronchitis or cough with persistent cold or flu-like illness that was not resolving. The term 'acute lower tract infection when pneumonia is not suspected' was also used to describe the clinical presentation. Trials that included people with pre-existing lung disease (e.g., acute exacerbation of chronic bronchitis) were excluded. The review pooled data for any antibiotic versus placebo, which are reported here.

Symptom severity

Antibiotics compared with placebo Antibiotics may be more effective than placebo at decreasing the proportion of people with cough and night cough. Antibiotics may also be more effective than placebo at decreasing the proportion of people with no improvement (measured by physician's global assessment) at 1 to 2 weeks; however, we don't know whether antibiotics are more effective than placebo at reducing days with impaired activities or 'feeling ill' (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cough					
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 4 RCTs in this analysis	**Proportion of people with cough , 1–2 weeks** 47/143 (33%) with antibiotics 67/132 (51%) with placebo	RR 0.64 95% CI 0.49 to 0.85 P = 0.0016	●○○	antibiotics
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 6 RCTs in this analysis	**Mean number of days with cough** with antibiotics with placebo 2350 people in this analysis	Mean difference –0.55 days 95% CI –1.00 days to –0.10 days P = 0.017	○○○	antibiotics
Productive cough					
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 6 RCTs in this analysis	**Proportion of people with productive cough , 7–18 days** 95/285 (33%) with antibiotics 96/264 (36%) with placebo	RR 0.88 95% CI 0.72 to 1.08 P = 0.23	⟷	Not significant
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis	**Mean duration of productive cough** with antibiotics with placebo	Mean difference –0.52 days 95% CI –1.03 days to –0.01 days The clinical importance of this result is unclear	○○○	antibiotics

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	5 RCTs in this analysis	535 people in this analysis			
Night cough					
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 4 RCTs in this analysis	**Proportion of people with night cough , 1–2 weeks** 80/271 (30%) with antibiotics 119/267 (45%) with placebo	RR 0.67 95% CI 0.54 to 0.83 P = 0.0003	●○○	antibiotics
Improvement					
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 11 RCTs in this analysis	**Clinically improved: proportion of people reporting no activity limitations or described as cured/globally improved** 1407/1922 (73%) with antibiotics 1277/1919 (67%) with placebo The 'clinically improved' composite outcome incorporates 'cure' (>75% reduction in the Acute Bronchitis Severity Score), global improvement or being well, patient report of no limitations, and resolution of symptoms rated as moderately bad, severe, or worsening	RR 1.07 95% CI 0.99 to 1.15 P = 0.077 Statistical heterogeneity: I^2 = 76%, P <0.00001 (see Further information on studies)	⟷	Not significant
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 5 RCTs in this analysis	**Proportion of people judged not to have improved (assessed by physician's global assessment) , 1–2 weeks** 32/413 (8%) with antibiotics 71/403 (18%) with placebo	RR 0.44 95% CI 0.30 to 0.65 P = 0.000036	●●○	antibiotics
Impaired activity					
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 5 RCTs in this analysis	**Proportion of people with activity limitations at follow-up , 1–2 weeks** 23/239 (10%) with antibiotics 34/239 (14%) with placebo	RR 0.75 95% CI 0.46 to 1.22 P = 0.25	⟷	Not significant
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 5 RCTs in this analysis	**Mean number of days with impaired activities** with antibiotics with placebo 393 people in this analysis	Mean difference –0.48 days 95% CI –0.96 days to +0.01 days P = 0.053	⟷	Not significant
Feeling ill					
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 4 RCTs in this analysis	**Mean number of days feeling ill** with antibiotics with placebo 435 people in this analysis	Mean difference –0.58 days 95% CI –1.16 days to 0 days P = 0.049 Result of borderline significance in favour of antibiotics	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity score					
[10] Systematic review	2061 adults, aged 18 years or over, lower respiratory tract infection, cough duration <28 days Data from 1 RCT	**Mean symptom severity scores (not further defined) , on days 2 to 4** 1.62 with amoxicillin 1.69 with placebo Further details not reported	P = 0.07	⟷	Not significant

Complications of acute bronchitis

No data from the following reference on this outcome. [10]

Quality of life

Antibiotics compared with placebo Azithromycin may be no more effective than placebo (vitamin C) at improving quality of life scores at 3 to 7 days in adults (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[10] Systematic review	220 adults, aged 18–88 years Data from 1 RCT	**Change in quality of life scores , at day 3 or day 7** with azithromycin with placebo (vitamin C) Absolute results not reported Both groups also received cough suppressant (dextromethorphan) and salbutamol (albuterol) inhaler	Reported as not significant	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] Systematic review	People of any age, including smokers but excluding people with chronic bronchitis 11 RCTs in this analysis	**Proportion of people with adverse effects** 367/1586 (23%) with antibiotics 295/1576 (19%) with placebo Adverse effects included nausea, vomiting or diarrhoea, headache, skin rash, and vaginitis	RR 1.22 95% CI 1.07 to 1.40 P = 0.0032 The review noted that side effects seemed mild, and 0% to 13% (overall 3.7%) of participants withdrew for this reason	●○○	placebo

Antibiotics versus inhaled beta$_2$ agonists:

See option on Inhaled beta$_2$ agonists, p 21 .

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Further information on studies

[10] The review noted that none of the summary outcomes exhibited statistically significant heterogeneity apart from the analysis on people who were 'clinically improved'. It did not comment further on the reason for statistical heterogeneity in this analysis. However, this was a composite outcome, and a sensitivity analysis removing the studies reporting no limitation of activities made no difference to the result. The review noted that all participants included in one RCT were tested for HIV. [11] It reported that only results for the subgroup who tested HIV negative were included in its analysis. The review reported that most RCTs used clinical findings to exclude people thought to have pneumonia, although four RCTs included chest X-rays. The specific antibiotic used varied between RCTs (including doxycycline, erythromycin, amoxicillin, co-amoxiclav, azithromycin, and trimethoprim/sulfamethoxazole).

[10] Of the 17 included RCTs, 15 were double-blinded or more. One single-blinded RCT included data for 280 participants. The remaining RCT was described as open label, but is not included in any of the analyses we have reported. The review reported that it was not able to obtain data for specific subgroups, so it did not carry out sensitivity analysis based on participant characteristics (age, duration, or smoking status).

Comment:

Subgroup analysis

We found two further follow-up reports [5] [12] of the largest RCT (2061 people; GRACE trial) included in the review, [10] which compared amoxicillin with placebo. The first report noted that, while adherence to antibiotic treatment in primary care was poor, on average 88.0% of prescribed amoxicillin in the trial was taken, as was 86.6% of placebo. [12] The second report presented a subgroup analysis of potential high-risk groups (green sputum, current smoker, significant past history [lung/heart disease, diabetes, hospital admission], fever at baseline, longer [>7 days] duration of illness) and reported on three main outcomes (resolution of symptoms rated moderately bad or worse, symptom severity score at days 2 to 4, and new or worsening of symptoms). [5] The report concluded that it found no clear evidence of a clinically meaningful benefit from antibiotics in the studied high-risk groups overall. Adverse events (nausea, diarrhoea, and rash) were more frequent in the amoxicillin arm (number needed to harm = 23). One individual in the amoxicillin arm experienced anaphylaxis. A subgroup analysis was performed in participants who were thought to be at greater risk: those with comorbidities (heart disease, lung disease, diabetes, and hospitalised in the previous year). Some subgroups had a significant, though at best modest, clinical benefit with amoxicillin for some outcomes but not for the other two outcomes. Those with comorbidities had a greater reduction in symptom severity at days 2 and 4 (P = 0.001). Those with green sputum and symptoms less than 7 days if they were non-smokers had a modest reduction in symptom severity at days 2 and 4 as well. Current smokers versus non-smokers had at best a modest reduction (P = 0.044) in resolution of symptoms compared with non-smokers, but no improvement in symptom severity at days 2 and 4. There was a risk with multiple comparisons in subgroups in this study, not all subgroups were pre-specified, and the study was not powered to detect rare but serious complications. [5]

Clinical guide

Physicians may be more likely to prescribe antibiotics for smokers with acute bronchitis than for non-smokers (90% in smokers *v* 75% in non-smokers; P <0.05). [13] However, the review reported that seven trials found no differences in antibiotic effectiveness for smokers versus non-smokers, but included no data on this in their original reports. [10] Many of the RCTs mentioned above diagnosed acute bronchitis on clinical grounds and commenced treatment independently of sputum culture results. It may be that isolation of a single organism on sputum culture could better identify people with a bacterial cause for their bronchitis, and thus identify a group that is more likely to benefit from antimicrobial therapy. However, sputum cultures are not generally used in the context of acute bronchitis. Relying on a clinical diagnosis of acute bronchitis is necessary, but the RCTs are likely to have included participants with a broad spectrum of illness. The RCTs did not differentiate on the basis of severity or duration of symptoms, and it is even possible that some people had mild pneumonia, because chest radiographs were not done universally to exclude this. Therefore, it is possible that a more severe subgroup exists, in which the benefit from antibiotics would be clearer. The systematic review found that, to prevent one person from having a cough at follow-up, the number needed to treat (NNT) would be 6 (95% CI not reported). [10] Given that treatment leads to a mean reduction in symptoms of less than 1 day compared with placebo, it is likely that this is of limited clinical relevance in most people, who will spontaneously improve anyway, albeit slightly more slowly. In addition, the potential small individual benefit from antibiotics must be weighed against the risk to the community that more widespread antibiotic use may increase bacterial resistance. [14]

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OPTION ANTIBIOTICS VERSUS EACH OTHER

- For GRADE evaluation of interventions for Bronchitis (acute), see table, p 28 .
- We don't know how different antibiotic regimens compare with each other, as we found insufficient evidence from RCTs.
- One review found that azithromycin (a macrolide) may be more effective than amoxicillin or amoxicillin plus clavulanic acid (co-amoxiclav) at reducing clinical failure in people with acute bronchitis. However, this analysis included two open-label studies, and evidence was weak.
- Widespread antibiotic use may lead to bacterial resistance to antibiotics.

Benefits and harms

Amoxicillin versus cephalosporins:

We found two RCTs. [15] [16] One RCT compared amoxicillin with cefuroxime, [15] and the other was a three-armed RCT [16] that compared amoxicillin plus clavulanic acid with cefuroxime given over 5 days or 10 days (see Further information on studies).

Symptom severity

Amoxicillin compared with cephalosporins Amoxicillin or amoxicillin plus clavulanic acid seem to be equally effective as cefuroxime (a cephalosporin) at increasing clinical cure rates and increasing satisfactory clinical outcomes (clinical cure or improvement) in people with clinically diagnosed acute bronchitis (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[15] RCT	296 adults with clinically diagnosed acute bronchitis and no pre-existing lung disease	**Clinical cure rates , 72 hours after last treatment** 123/153 (80%) with amoxicillin 109/143 (76%) with cefuroxime Antibiotics were given daily for 7 consecutive days	P = 0.8	⟷	Not significant
Satisfactory clinical outcome					
[16] RCT **3-armed trial**	537 people aged at least 12 years with clinically diagnosed acute bronchitis and no pre-existing lung disease	**Proportion of people with satisfactory clinical outcome (clinical cure or improvement) , up to 15 days after treatment** 130/183 (71%) with amoxicillin plus clavulanic acid (given for 10 days) 107/177 (60%) with cefuroxime axetil (given for 5 days, after which placebo given for 5 days) Satisfactory clinical outcome was defined as the sum of clinical cure (complete resolution of clinical signs and symptoms of infection at 1 to 3 days, and 13 to 15 days after treatment) and clinical improvement (clinical signs and symptoms substantially reduced but not completely resolved) The remaining arm evaluated cefuroxime axetil given for 10 days	P = 0.91	⟷	Not significant
[16] RCT **3-armed trial**	537 people aged at least 12 years with clinically diagnosed acute bronchitis and no pre-existing lung disease	**Proportion of people with satisfactory clinical outcome (clinical cure or improvement) after treatment , up to 15 days after treatment**	P = 0.45	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		130/183 (71%) with amoxicillin plus clavulanic acid (given for 10 days) 117/177 (66%) with cefuroxime axetil (given for 10 days) Satisfactory clinical outcome was defined as the sum of clinical cure (complete resolution of clinical signs and symptoms of infection at 1 to 3 days, and 13 to 15 days after treatment) and clinical improvement (clinical signs and symptoms substantially reduced but not completely resolved) The remaining arm evaluated cefuroxime axetil given for 5 days (after which placebo given for 5 days)			

Complications of acute bronchitis

No data from the following reference on this outcome. [15] [16]

Quality of life

No data from the following reference on this outcome. [15] [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[16] RCT **3-armed trial**	537 people aged at least 12 years with clinically diagnosed acute bronchitis and no pre-existing lung disease	**Proportion of people with at least 1 treatment-related adverse event** 71/183 (39%) with amoxicillin plus clavulanic acid (given for 10 days) 41/177 (23%) with cefuroxime axetil (given for 5 days, after which placebo given for 5 days) 41/177 (23%) with cefuroxime axetil (given for 10 days) See Further information on studies	P = 0.001 (for amoxicillin plus clavulanic acid *v* either cefuroxime given for 5 days or given for 10 days)	○○○	cefuroxime

No data from the following reference on this outcome. [15]

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Macrolides versus amoxicillin:

We found one systematic review (search date 2014), [17] which identified six RCTs comparing azithromycin with amoxicillin or amoxicillin plus clavulanic acid (co-amoxiclav) in people with acute bronchitis and pooled data. However, five of these RCTs did not meet the inclusion criteria for this *BMJ Clinical Evidence* overview. We have, therefore, reported the RCT that met our criteria below, and have reported the pooled data in Further information on studies. We also found one RCT comparing roxithromycin with amoxicillin. [18]

Symptom severity

Macrolides compared with amoxicillin We don't know whether azithromycin is more effective than amoxicillin or amoxicillin plus clavulanic acid (co-amoxiclav) at reducing the proportion of people with clinical failure at 10 to 14 days after start of treatment in people with clinical evidence of acute bronchitis. We don't know how roxithromycin (a macrolide) and amoxicillin compare at increasing the proportion of people with physician-assessed improvement or cure in adults with clinically diagnosed acute bronchitis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[17] Systematic review	People aged 18 years or older with acute bronchitis with suspected bacterial cause Data from 1 RCT Subgroup analysis	**Proportion of people with clinical failure (persistence or deterioration of symptoms, death, or relapse) , days 10–14 after start of treatment** 4/113 (3.5%) with azithromycin 3/115 (2.6%) with amoxicillin or amoxicillin plus clavulanic acid (co-amoxiclav) The trial included people with acute bronchitis, chronic bronchitis, or pneumonia The review extracted data for the 228/369 (62%) people with acute bronchitis only	RR 1.36 95% CI 0.31 to 5.93	⟷	Not significant
[18] RCT	196 adults with clinically diagnosed acute bronchitis and no pre-existing lung disease	**Proportion of people with physician-assessed improvement or cure** 89/96 (93%) with roxithromycin 88/96 (92%) with amoxicillin Antibiotics were given for 10 days	P = 0.8	⟷	Not significant

Complications of acute bronchitis

No data from the following reference on this outcome. [17] [18]

Quality of life

No data from the following reference on this outcome. [17] [18]

Adverse effects

No data from the following reference on this outcome. [17] [18]

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Macrolides versus each other:

We found one RCT comparing azithromycin versus clarithromycin. [19]

Symptom severity

Macrolides compared with each other Azithromycin and clarithromycin seem equally effective at increasing clinical cure rates at 6 to 7 days in adults with clinically diagnosed acute bronchitis (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rate					
[19] RCT	214 adults with clinically diagnosed acute bronchitis and no pre-existing lung disease	**Clinical cure rates , 6–7 days** 55/103 (53%) with azithromycin 70/108 (65%) with clarithromycin Antibiotics were given for 5 days See Further information on studies for details of relapse rates	P = 0.4	⟷	Not significant

Complications of acute bronchitis

No data from the following reference on this outcome. [19]

Quality of life

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT	214 adults with clinically diagnosed acute bronchitis and no pre-existing lung disease	**Adverse effects** 17/105 (16%) with azithromycin 13/109 (12%) with clarithromycin Antibiotics were given for 5 days	P = 0.56	⟷	Not significant

Cephalosporins versus each other:

We found two RCTs. [20] [21]

Symptom severity

Cephalosporins compared with each other We don't know whether cephalosporins differ in their effectiveness at improving satisfactory clinical outcomes (not further defined) in people with clinically diagnosed acute bronchitis (moderate-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical improvement					
[20] RCT	465 children aged <12 years with clinically diagnosed acute bronchitis and no pre-existing lung disease	**Proportion of people with satisfactory clinical outcome, as assessed by the treating general practitioner , 14 days** 130/148 (88%) with cefuroxime 217/238 (91%) with cefixime No further definition of 'satisfactory clinical outcome' reported Antibiotics were given for 10 days	P = 0.8	⟷	Not significant
[21] RCT	196 older people with clinically diagnosed acute purulent bronchitis and no pre-existing lung disease	**Proportion of people with physician-rated satisfactory clinical response , 10 days** 86/95 (91%) with cefuroxime 87/92 (95%) with cefpodoxime No further definition of 'satisfactory clinical outcome' reported Antibiotics were given for 5 days	P = 0.76	⟷	Not significant

Complications of acute bronchitis

No data from the following reference on this outcome. [20] [21]

Quality of life

No data from the following reference on this outcome. [20] [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT	196 older people with clinically diagnosed acute purulent bronchitis and no pre-existing lung disease	**Adverse effects** 4/95 (4%) with cefuroxime 6/92 (7%) with cefpodoxime	Significance not assessed		

No data from the following reference on this outcome. [20]

Further information on studies

[19] The RCT found no significant difference between azithromycin and clarithromycin in relapse rate after 6 to 7 days (2/95 [2%] with azithromycin *v* 1/101 [1%] with clarithromycin; P = 0.5).

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[16] Two of the eight authors of this RCT were employees of the pharmaceutical company sponsoring the study. The RCT reported that there were significantly more people with one or more drug-related gastrointestinal adverse effects with amoxicillin plus clavulanic acid (67/183 [37%]) compared with cefuroxime axetil given for 5 days (34/177 [19%], P <0.001) and 10 days (26/177 [15%], P <0.001). However, there were significantly more people with one or more drug-related female genitalia adverse effects with cefuroxime axetil given for 10 days compared with amoxicillin plus clavulanic acid (5/177 [5%] *v* 0/183 [0%], P = 0.027).

[17] The review included 16 RCTs in people with acute lower respiratory tract infections (including people with acute bronchitis, pneumonia, and exacerbations of chronic bronchitis). It reported a subgroup analysis on acute bronchitis alone. It found that azithromycin significantly reduced clinical failure compared with amoxicillin or amoxicillin plus clavulanic acid (co-amoxiclav) (6 RCTs, 63/738 [9%] with azithromycin *v* 65/558 [12%] with amoxicillin or co-amoxiclav, RR 0.63, 95% CI 0.45 to 0.88). However, the two largest RCTs, which also found the largest treatment effects in favour of azithromycin (comprising 858/1296 [66%] of participants in the analysis), were open-label studies, which is outside the inclusion criteria of this *BMJ Clinical Evidence* overview (double-blind). Among the other four RCTs, in one RCT 39/102 (38%) of participants were described as having acute exacerbations of chronic bronchitis, one RCT only contributed seven people to the analysis, and one was single blinded. We have reported the remaining RCT, which met our inclusion criteria, in the main benefits section above. Of the six included RCTs in the analysis, most did not describe the method of randomisation or allocation concealment, and the review noted that two RCTs were at high risk of bias for allocation concealment (selection bias). [17]

[17] Twelve RCTs included in the review reported adverse effects. The most frequent adverse events were mild to moderate gastrointestinal symptoms, nausea, vomiting, and diarrhoea. The other reported adverse effects were headache, insomnia, rash, and transient laboratory liver function changes. The overall incidence of adverse events in the azithromycin group was 244/1363 (18%), compared with 246/1043 (24%) in the amoxicillin or co-amoxiclav group (RR 0.76, 95% CI 0.57 to 1.00, P = 0.047). One large RCT also reported a higher number of participants stopping co-amoxiclav treatment because of adverse effects, compared with the azithromycin group (7% with co-amoxiclav *v* 1.2% with azithromycin).

Comment:

Clinical guide

The overall effect of antibiotics on acute bronchitis is small. In comparing antibiotic classes, there have been limited comparisons, and not all potential antibiotic combinations have been studied. It is possible that more severe subgroups of patients exist in whom the benefits of antibiotics would be greater, but this cannot be determined from the current clinical trials. Antibiotics are associated with side effects, and their widespread use will worsen microbial resistance patterns.

It is not clear whether macrolides have their effect as antimicrobial agents or through an anti-inflammatory mechanism, which is possible and has been proposed in reference to their role in bronchiectasis and in reducing exacerbations of chronic obstructive pulmonary disease (COPD) and other chronic respiratory diseases. [22]

See Comment section in Antibiotics versus placebo and other treatments, p 4 .

OPTION ANTIHISTAMINES

- For GRADE evaluation of interventions for Bronchitis (acute), see table, p 28 .
- We don't know whether antihistamines improve symptoms of acute bronchitis compared with placebo, as we found few good-quality trials.

Benefits and harms

Antihistamines versus placebo:

We found one systematic review of non-prescription medications in people with acute cough (search date 2014). [23] The review did not perform any meta-analyses because of heterogeneity among trials and lack of quantitative data reported by most trials identified. It identified five RCTs of antihistamines that met our inclusion criteria (2 in adults [24] [25] and 3 in children [23] [26] [27]). The three RCTs in children all compared three interventions: the first compared the antihistamines clemastine or chlorpheniramine for 3 days with placebo; [26] the second compared the antihistamine diphenhydramine or the antitussive dextromethorphan with placebo; [27] and the third compared the antihistamine promethazine or the antitussive dextromethorphan with placebo. [23]

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Symptom severity

Antihistamines compared with placebo Antihistamines may be no more effective than placebo at reducing mean cough scores at 3–4 days in adult non-smokers or children with acute bronchitis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cough					
[24] RCT	100 adult non-smokers In review [23] See Further information on studies for details of population criteria set by review	**Mean cough score (range 0–3, higher scores indicating worse cough) , 4 days** 0.80 with terfenadine 0.65 with placebo	P = 0.35	⟷	Not significant
[25] RCT	250 adult non-smokers In review [23] See Further information on studies for details of population criteria set by review	**Self-reported symptom scores for cough , 3 days** with terfenadine with placebo Absolute results not reported	Reported as not significant No further data reported; the trial was designed to assess overall effects on common cold symptoms	⟷	Not significant
[26] RCT **3-armed trial**	150 children In review [23] See Further information on studies for details of population criteria set by review	**Proportion of people with improvement in cough scores as observed by physicians and participants , 3 days** 19/48 (40%) with clemastine 19/48 (40%) with chlorpheniramine 13/47 (28%) with placebo There was spontaneous improvement in all groups	P = 0.20 for either antihistamine *v* placebo	⟷	Not significant
[27] RCT **3-armed trial**	100 children In review [23] See Further information on studies for details of population criteria set by review	**Mean improvement in cough frequency score (score range 0–6, higher score indicates more severe cough) , 3 days** 1.97 with diphenhydramine 2.24 with placebo 77 children in this analysis The remaining arm assessed dextromethorphan	P = 0.56	⟷	Not significant
[23] Systematic review	120 participants aged 1–22 years, mean age 5 years Data from 1 RCT 3-armed RCT See Further information on studies for details of population criteria set by review	**Cough and sleep-related outcomes (not further defined in review)** with promethazine with placebo Absolute results not reported The remaining arm assessed dextromethorphan	Reported as "no difference from placebo"		

Complications of acute bronchitis

No data from the following reference on this outcome. [23]

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Quality of life

No data from the following reference on this outcome. [23]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] Systematic review	See Further information on studies for details of population criteria set by review 4 RCTs in this analysis	**Adverse effects** with antihistamines with placebo In one RCT in adults, possible adverse effects were rare in both groups (6.1% with terfenadine *v* 4% with placebo); in another in adults, the most common adverse effect was excess fatigue (12% with terfenadine *v* 10% with placebo); one RCT in children comparing clemastine, chlorpheniramine, and placebo reported drowsiness in 20% of children with "no difference between the groups", while another RCT in children reported that 13 children had adverse effects with promethazine versus two children with placebo (further details and statistical analysis not reported)			

Further information on studies

[23] The systematic review stated that it examined the effects of treatments in people with 'upper respiratory tract infection' rather than 'acute bronchitis'. However, the clinical criteria used to define this population were consistent with the definition of acute bronchitis used in this overview. The review included children and adults with acute onset of cough (<3 weeks' duration) and excluded studies in chronic cough (>3 weeks' duration), underlying respiratory diseases (such as asthma, COPD, pneumonia, tuberculosis, lung malignancy), and in people with artificially induced cough. Overall, including all interventions, the review identified 29 RCTs of various non-prescription medications: 12 of these RCTs were wholly or partly funded by the pharmaceutical industry; eight of these 12 RCTs found positive results, whereas only four out of 15 independent RCTs demonstrated a positive result.

Comment: In all trials identified by the review, the symptoms described seemed to be very mild; both active and placebo groups tended to improve in the short time frame examined. [23]

OPTION ANTITUSSIVES

- For GRADE evaluation of interventions for Bronchitis (acute), see table, p 28 .
- We don't know whether antitussives improve symptoms of acute bronchitis compared with placebo, as we found few good-quality trials.

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Benefits and harms

Dextromethorphan versus placebo:

We found two systematic reviews (search dates 2014 [23] and 2011 [28]). The first review compared non-prescription medications with placebo in people with acute cough. [23] The review did not perform any meta-analyses because of heterogeneity among trials and lack of quantitative data reported by most trials identified. It identified one RCT [29] and one non-systematic review [30] (see Comment, p 15) assessing dextromethorphan in adults. The first review also identified four RCTs assessing dextromethorphan in children. [23] [27] [31] [32] The second review [28] compared beta$_2$ agonists with placebo in people with acute bronchitis, and identified one additional RCT in children that was also identified in the first review. [32]

Symptom severity

Dextromethorphan compared with placebo We don't know how dextromethorphan and placebo compare at reducing cough scores or improving clinical condition in adults or children with acute bronchitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cough					
[29] RCT	44 adults In review [23]	**Mean decline in cough score (range 0–3, higher score indicating more severe cough) , 3 days** 1.0 with dextromethorphan 0.5 with placebo	P = 0.8	⟷	Not significant
[31] RCT **3-armed trial**	57 children In review [23]	**Mean reduction in cough score (range 0–4, higher score indicating more severe cough) , 3 days** 2.1 with dextromethorphan 2.2 with placebo Dextromethorphan was given at bedtime for 3 nights 32 children in this analysis The remaining arm evaluated codeine	P = 0.40 for dextromethorphan *v* placebo	⟷	Not significant
[32] RCT **3-armed trial**	75 children with acute bronchitis or acute cough In review [23] [28]	**Mean cough score , day 3** 0.60 with dextromethorphan 0.76 with placebo Dextromethorphan was given at a dose of 7.5 mg once daily for children aged <7 years and 15 mg once daily for children 7 years and over 50 children in this analysis The third arm evaluated dextromethorphan plus salbutamol	Reported as not significant; also reported as not significant at days 1 and 2 P values not reported	⟷	Not significant
[27] RCT **3-armed trial**	100 children In review [23] See Further information on studies for details of population criteria set by review	**Mean improvement in cough frequency score (score range 0–6, higher score indicates more severe cough) , 3 days** 1.97 with dextromethorphan 2.24 with placebo Absolute numbers not reported 77 children in this analysis The remaining arm assessed diphenhydramine	P = 0.56	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical condition					
[32] RCT **3-armed trial**	75 children with acute bronchitis or acute cough In review [23] [28]	**Mean general condition score , day 3** 2.00 with dextromethorphan 2.08 with placebo Dextromethorphan was given at a dose of 7.5 mg once daily for children aged <7 years and 15 mg once daily for children 7 years and over 50 children in this analysis The third arm evaluated dextromethorphan plus salbutamol	Reported as not significant; also reported as not significant at days 1 and 2 P values not reported	⟷	Not significant
[32] RCT **3-armed trial**	75 children with acute bronchitis or acute cough In review [23] [28]	**Proportion of children reporting some or marked relief** 16/24 (67%) with dextromethorphan 19/24 (73%) with placebo Dextromethorphan was given at a dose of 7.5 mg once daily for children aged <7 years and 15 mg once daily for children 7 years and over 50 children in this analysis The third arm evaluated dextromethorphan plus salbutamol	Reported as not significant P value not reported	⟷	Not significant
[23] Systematic review	120 participants aged 1–22 years, mean age 5 years Data from 1 RCT 3-armed RCT See Further information on studies for details of population criteria set by review	**Mean composite symptom score (not further defined) , day 3** 4.6 with dextromethorphan 5.0 with placebo 80 children in this analysis The third arm assessed promethazine	Reported as not significant P value not reported	⟷	Not significant

Complications of acute bronchitis

No data from the following reference on this outcome. [23] [27] [29] [31] [32]

Quality of life

No data from the following reference on this outcome. [23] [27] [29] [31] [32]

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31] RCT **3-armed trial**	57 children In review [23]	**Proportion of children with adverse effects** 6/19 (31%) with dextromethorphan 7/13 (54%) with placebo Dextromethorphan was given at bedtime for 3 nights Adverse effects included drowsiness, diarrhoea, and hyperactive behaviour The remaining arm evaluated codeine	Significance not assessed		
[32] RCT **3-armed trial**	75 children with acute bronchitis or acute cough In review [23] [28]	**Proportion of children with serious adverse effects** 3/24 (13%) with dextromethorphan 1/26 (4%) with placebo Dextromethorphan was given at a dose of 7.5 mg once daily for children aged <7 years and 15 mg once daily for children 7 years and over The third arm evaluated dextromethorphan plus salbutamol	Reported as not significant P value not reported	⟷	Not significant
[23] Systematic review	120 participants aged 1–22 years, mean age 5 years Data from 1 RCT 3-armed RCT See Further information on studies for details of population criteria set by review	**Adverse effects (not further defined)** 34% with dextromethorphan 5% with placebo Absolute numbers not reported The third arm assessed promethazine	Significance not reported		

No data from the following reference on this outcome. [27] [29]

Codeine versus placebo:

We found one systematic review (search date 2014). [23] The review compared non-prescription medications with placebo in people with acute cough. [23] The review did not perform any meta-analyses because of heterogeneity among trials and lack of quantitative data reported by most trials identified. It identified two RCTs assessing codeine in adults, [33] [34] and one RCT in children [31] that met our inclusion criteria. We have reported directly from the RCTs.

Symptom severity

Codeine compared with placebo Codeine may be no more effective than placebo at reducing cough severity scores at up to 5 days in adults and children (very low-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cough					
[33] RCT	81 adults In review [23]	**Mean cough severity score (higher score indicates worse cough, scale end points unclear) , 5 days** 17.2 with codeine 18.0 with placebo	P = 0.5	⟷	Not significant
[34] RCT	82 adults In review [23]	**Change in subjective cough severity score (5-point rating scale) , 90 minutes after treatment** from 2.0 to 1.0 with codeine from 2.0 to 1.0 with placebo	P = 0.80	⟷	Not significant
[31] RCT **3-armed trial**	57 children In review [23]	**Mean reduction in cough score (range 0–4, higher score indicating more severe cough) , 3 days** 2.2 with codeine 2.2 with placebo Codeine was given at bedtime for 3 nights 30 children in this analysis The remaining arm evaluated dextromethorphan	P = 0.70 for codeine *v* placebo	⟷	Not significant

Complications of acute bronchitis

No data from the following reference on this outcome. [31] [33] [34]

Quality of life

No data from the following reference on this outcome. [31] [33] [34]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31] RCT **3-armed trial**	57 children In review [23]	**Proportion of children with adverse effects** 5/17 (29%) with codeine 7/13 (54%) with placebo Dextromethorphan was given at bedtime for 3 nights Adverse effects included diarrhoea and hyperactive behaviour The remaining arm evaluated dextromethorphan	Significance not assessed		

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No data from the following reference on this outcome. [33] [34]

Moguisteine versus placebo:

We found one systematic review (search date 2014), [23] which compared non-prescription medications with placebo in people with acute cough. The review identified one RCT in adults. [35]

Symptom severity

Moguisteine compared with placebo Moguisteine may be modestly more effective than placebo at reducing mean cough severity scores in adults, but this is based on limited evidence from one RCT (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cough					
[35] RCT	108 adults In review [23]	**Cough severity score (scale 0–9, higher score indicating more severe cough)** with moguisteine with placebo Absolute results not reported Moguisteine is available without prescription only in the UK	Mean difference in cough score 0.5 P <0.05	○○○	moguisteine

Complications of acute bronchitis

No data from the following reference on this outcome. [35]

Quality of life

No data from the following reference on this outcome. [35]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[35] RCT	108 adults In review [23]	**Proportion of people reporting nausea, vomiting, and abdominal pain** 10 events in 54 people with moguisteine 3 events in 51 people with placebo Moguisteine is available without prescription only in the UK	P <0.05	○○○	placebo

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Further information on studies

[23] The review stated that it examined the effects of treatments in people with acute cough due to 'upper respiratory tract infection' rather than 'acute bronchitis'. However, the clinical criteria used to define this population were consistent with the definition of acute bronchitis used in this overview. The review included children and adults with acute onset of cough (<3 weeks' duration) and excluded studies in chronic cough (>3 weeks' duration), underlying respiratory diseases (such as asthma, COPD, pneumonia, tuberculosis, lung malignancy), and in people with artificially induced cough. Overall, including all interventions, the review identified 29 RCTs of various non-prescription medications: 12 of these RCTs were wholly or partly funded by the pharmaceutical industry; eight of these 12 RCTs found positive results, whereas only four out of 15 independent RCTs demonstrated a positive result.

Comment: The systematic review [23] identified one 'non-systematic' review. [30] This collated data from three RCTs (451 adults) on cough acoustic signals captured via microphone, over 3 hours. Percentage difference in number of cough bouts between dextromethorphan and placebo ranged from 19% in two RCTs to 36% in one RCT. There was significantly less cough with dextromethorphan (single dose) compared with placebo (P <0.05, absolute results not reported). However, the clinical relevance of this outcome is unclear as cough was measured in a controlled environment over a very short timeframe.

Clinical guide
Moguisteine is available without prescription only in the UK.

OPTION BETA2 AGONISTS (INHALED)

- For GRADE evaluation of interventions for Bronchitis (acute), see table, p 28 .
- We don't know whether inhaled $beta_2$ agonists improve symptoms of acute bronchitis compared with placebo, as we found few good-quality trials.
- We found no direct results from RCTs about inhaled $beta_2$ agonists in the treatment of children with acute bronchitis.

Benefits and harms

Inhaled $beta_2$ agonists versus placebo:

We found one systematic review (search date 2011), [28] which identified two RCTs of inhaled $beta_2$ agonists in 126 adults, both smokers and non-smokers, with acute bronchitis or acute cough. People with pre-existing lung disease, or with another acute respiratory disorder, were excluded. The review carried out a meta-analysis that combined results for oral and inhaled $beta_2$ agonists (salbutamol and fenoterol) versus placebo in adults. [28]

Symptom severity

Inhaled $beta_2$ agonists compared with placebo We don't know whether inhaled $beta_2$ agonists are more effective than placebo at reducing the proportion of adults with cough at 7 days or at increasing the proportion of people able to work at 4 days (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cough					
[28] Systematic review	People with acute bronchitis or acute cough 3 RCTs in this analysis	**Proportion of adults with cough , 7 days** 70/110 (64%) with $beta_2$ agonists 78/110 (71%) with placebo This analysis included 119 people from 2 RCTs of inhaled $beta_2$ agonists, and 101 people from 1 RCT of oral $beta_2$ agonists	RR 0.86 95% CI 0.63 to 1.18 Heterogeneity: I^2 = 63%, P = 0.07	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Impaired activities					
[28] Systematic review	Adults with acute bronchitis or acute cough 2 RCTs in this analysis	**Proportion of adults unable to work , 4 days** 22/76 (29%) with beta$_2$ agonists 23/73 (32%) with placebo This analysis included 46 people from 1 RCT of inhaled beta$_2$ agonists, and 103 people from 1 RCT of oral beta$_2$ agonists	RR 0.82 95% CI 0.28 to 2.34 Heterogeneity: I^2 = 74%, P = 0.05	⟷	Not significant

Complications of acute bronchitis

No data from the following reference on this outcome. [28]

Quality of life

No data from the following reference on this outcome. [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] Systematic review	People with acute bronchitis or acute cough Data from 1 RCT	**Shaking and tremor** 18/37 (49%) with inhaled beta$_2$ agonists 0/36 (0%) with placebo	RR 36.0 95% CI 2.3 to 576.3	●●●	placebo

Inhaled beta$_2$ agonists versus antibiotics:

We found one systematic review (search date 2011), which identified no RCTs in children or adults. [28]

Comment: None.

OPTION EXPECTORANTS AND MUCOLYTICS

- For GRADE evaluation of interventions for Bronchitis (acute), see table, p 28 .
- We don't know whether expectorants and mucolytics improve symptoms of acute bronchitis compared with placebo, as we found few good-quality trials.

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Benefits and harms

Expectorants and mucolytics versus placebo:

We found two systematic reviews (search dates 2014 [23] and 2013 [36]). The first review [23] assessed non-prescription medications in people with acute cough, and identified four RCTs. The second review [36] assessed the mucolytics acetylcysteine and carbocysteine in children younger than 18 years with acute respiratory tract infection, and identified one RCT that met our inclusion criteria (see Further information on studies for populations included in the two reviews). We found two additional RCTs. [37] [38]

Symptom severity

Expectorants and mucolytics compared with placebo We don't know how effective expectorants and mucolytics are compared with placebo in reducing symptoms in adults and children with acute bronchitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cough					
[23] Systematic review	239 adults with acute upper respiratory tract infection Data from 1 RCT	**Proportion of people who reported treatment was 'helpful' in reducing cough intensity and frequency , 72 hours** 79/105 (75%) with guaifenesin 33/106 (31%) with placebo Assessed by patient questionnaire; cough scored on scale of 0–3, unclear how the results were dichotomised to calculate number of people finding treatment 'helpful'	P <0.01	○○○	guaifenesin
[23] Systematic review	99 adults working in a chemical factory who had acute upper respiratory tract infection Data from 1 RCT	**Proportion of people with frequent cough (defined as cough every 2–4 minutes)** 4/46 (9%) with bromhexine plus ammonium chloride (Bisolvon linctus) 7/46 (15%) with placebo Unclear how outcome was recorded	P <0.02	○○○	bromhexine
[23] Systematic review	40 children with acute febrile bronchitis Data from 1 RCT	**Reduction in cough scores (measured on a scale from 0–3) , days 4–10** with letosteine with placebo Unclear how outcome was measured; see Further information for details about intervention	Difference between groups ranging from 0.1 to 0.3 points P <0.01	○○○	letosteine
[36] Systematic review	48 children (age >2 years) with acute bronchitis Data from 1 RCT Subgroup analysis	**Cough at end of treatment , 28 days** 2/27 (7%) with acetylcysteine 3/21 (14%) with placebo	Risk difference –0.07 95% CI –0.25 to +0.11 RR 0.52 95% CI 0.10 to 2.83	⟷	Not significant
[36] Systematic review	48 children (age >2 years) with acute bronchitis Data from 1 RCT Subgroup analysis	**Cough productivity at end of treatment , 28 days** 2/27 (7%) with acetylcysteine 3/21 (14%) with placebo	Risk difference –0.07 95% CI –0.25 to +0.11 RR 0.52 95% CI 0.10 to 2.83	⟷	Not significant
[37] RCT	363 adults with acute bronchitis See Further information on studies	**Mean reduction in cough frequency (assessed by subjective counting of coughing fits during the day) , 9 days**	P <0.001	○○○	thyme-ivy syrup

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	for full details of population included in RCT	78% with oral thyme-ivy syrup (Bronchipret Saft) 56% with placebo Absolute numbers not reported			
[38] RCT	242 adults (age 18–70 years) with acute bronchitis for not longer than 7 days	**Decrease in mean frequency of coughing fits (6-point scale, where 0 = none to 5 = >15 coughing fits per day) , 4 days** 1.18 with cineole 0.64 with placebo	P = 0.0001 See Further information on studies	○○○	cineole
[38] RCT	242 adults (age 18–70 years) with acute bronchitis for not longer than 7 days	**Decrease in cough measured by cough documentation (7-point scale, where 0 = no cough to 6 = continuously during whole day) , 4 days** 1.3 with cineole 1.0 with placebo	P = 0.0869 See Further information on studies	⟷	Not significant
Overall symptoms					
[36] Systematic review	48 children (age >2 years) with acute bronchitis Data from 1 RCT Subgroup analysis	**'Thoracic semeiologic alterations' (i.e., wheezing breathing, rattling) , at end of treatment, 28 days** 1/27 (4%) with acetylcysteine 3/21 (14%) with placebo	Risk difference –0.11 95% CI –0.27 to +0.06 RR 0.26 95% CI 0.03 to 2.32	⟷	Not significant
[37] RCT	363 adults with acute bronchitis See Further information on studies for full details of population included in RCT	**Overall symptoms (assessed by Bronchitis Severity Score [BSS]) , 9 days** with oral thyme-ivy syrup (Bronchipret Saft) with placebo Absolute results reported graphically	P <0.001	○○○	thyme-ivy syrup
[23] Systematic review	378 participants aged >12 years Data from 1 RCT	**Total spontaneous symptom severity score (8-item composite symptom score), reduction in mean score , from baseline to day 4** 7.1 with guaifenesin 5.7 with placebo	P = 0.04	○○○	guaifenesin
[23] Systematic review	378 participants aged >12 years Data from 1 RCT	**Total spontaneous symptom severity score (8-item composite symptom score) , day 7** with guaifenesin with placebo Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Complications of acute bronchitis

No data from the following reference on this outcome. [23] [36] [37]

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Quality of life

No data from the following reference on this outcome. [23] [36] [37]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] RCT	363 adults with acute bronchitis See Further information on studies for full details of population included in RCT	**Proportion of people with an adverse effect , 9 days** 7/183 (4%) with oral thyme-ivy syrup (Bronchipret Saft) 8/179 (5%) with placebo	Significance not assessed		
[38] Systematic review	242 adults (age 18–70 years) with acute bronchitis for not longer than 7 days	**Adverse effects** with cineole with placebo Absolute results not reported	Reported as not significant P value not reported One adverse effect was thought to be related to placebo (heartburn and burning mouth) and one to cineole (stomach aches)	⟷	Not significant

No data from the following reference on this outcome. [23] [36]

Further information on studies

[23] The systematic review stated that it examined the effects of treatments in people with 'upper respiratory tract infection' rather than 'acute bronchitis'. However, the clinical criteria used to define this population were consistent with the definition of acute bronchitis used in this overview. The review included children and adults with acute onset of cough (<3 weeks' duration) and excluded studies in chronic cough (>3 weeks' duration), underlying respiratory diseases (such as asthma, COPD, pneumonia, tuberculosis, lung malignancy), and in people with artificially induced cough. Overall, including all interventions, the review identified 29 RCTs of various non-prescription medications: 12 of these RCTs were wholly or partly funded by the pharmaceutical industry; eight of these 12 RCTs found positive results, whereas only four out of 15 independent RCTs demonstrated a positive result. One of the included RCTs assessed letosteine; this preparation is not available in the UK and several other parts of the world.

[36] The systematic review assessed the effects of acetylcysteine and carbocysteine (mucolytics) in children aged less than 18 years with a physician diagnosis of acute respiratory tract infection (e.g., acute pneumonia, acute bronchitis, acute bronchiolitis, acute cough) without chronic broncho-pulmonary disease. The review carried out a subgroup analysis of participants in the RCTs with acute bronchitis. One RCT was included in this subgroup analysis. Participants in this RCT were allowed antibiotics if required.

[37] In the additional RCT, the study population was defined as people with acute bronchitis and productive cough and, although chest radiographs were not done, the participants' characteristics are consistent with a diagnosis of acute bronchitis and not of mild acute pneumonia.

[38] The RCT also reported a non-standard composite bronchitis sum score, which included elements of symptoms (dyspnoea, sputum, cough, pain), clinical examination (auscultation score), and lung function, which we have not reported further.

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Comment: **Clinical guide**
There is little evidence that expectorants and mucolytics improve symptoms of acute bronchitis compared with placebo, with few good-quality trials in either adults or children. At this stage there is insufficient evidence to recommend their use.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antibiotics versus each other One systematic review added. [17] Categorisation unchanged (unknown effectiveness).

Antibiotics versus placebo and other non-antibiotic treatments Two subsequent reports of one RCT included in the review. [5] [12] One systematic review updated. [10] Categorisation unchanged (trade-off between benefits and harms).

Antihistamines One systematic review updated. [23] Categorisation unchanged (unknown effectiveness).

Antitussives One systematic review updated. [23] Categorisation unchanged (unknown effectiveness).

Beta$_2$ agonists (inhaled) One systematic review updated. [28] Categorisation unchanged (unknown effectiveness).

Expectorants and mucolytics One systematic review added, [36] one updated, [23] and one additional RCT added. [38] Categorisation unchanged (unknown effectiveness).

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Competing interests: PW has been reimbursed for attending international and national scientific meetings by AstraZeneca, GlaxoSmithKline, and Novartis. He has also received consulting fees from AstraZeneca in work in reference to asthma and the use of the product Symbicort. In addition, he has received consulting fees from Boehringer Ingelheim for the use of tiotropium in asthma.

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GRADE **Evaluation of interventions for Bronchitis (acute).**

Important outcomes			Adverse effects, Complications of acute bronchitis, Quality of life, Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for acute bronchitis in people without chronic respiratory disease?									
At least 11 (at least 3841) [10]	Symptom severity	Antibiotics versus placebo	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity amongst RCTs; directness point deducted for use of subjective/surrogate outcomes
1 (220) [10]	Quality of life	Antibiotics versus placebo	4	0	0	–3	0	Very low	Directness points deducted for small number of comparators, restricting population to adults, and allowing use of non-study medication (cough suppressant and salbutamol [albuterol] inhaler)
2 (833) [15] [16]	Symptom severity	Amoxicillin versus cephalosporins	4	0	0	–1	0	Moderate	Directness point deducted for small number of comparators
2 (424) [17] [18]	Symptom severity	Macrolides versus amoxicillin	4	–1	0	–1	0	Low	Quality point deducted for subgroup analysis; directness point deducted for small number of comparators
1 (214) [19]	Symptom severity	Macrolides versus each other	4	0	0	–1	0	Moderate	Directness point deducted for small number of comparators
2 (573) [20] [21]	Symptom severity	Cephalosporins versus each other	4	0	0	–1	0	Moderate	Directness point deducted for use of unclear outcomes
5 (at least 703) [23] [24] [25] [26] [27]	Symptom severity	Antihistamines versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting; directness point deducted for very short follow-up
5 (283) [23] [27] [29] [31] [32]	Symptom severity	Dextromethorphan versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results; directness points deducted for assessment of outcomes with unclear clinical relevance and for very short follow-up in the largest included trial
3 (193) [31] [33] [34]	Symptom severity	Codeine versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for sparse data; directness points deducted for very short follow-up in 1 RCT and unclear scoring system for outcome measurement in another RCT
1 (108) [35]	Symptom severity	Moguisteine versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for unclear clinical importance
At least 3 (at least 220) [28]	Symptom severity	Inhaled beta$_2$ agonists versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for combining data for both oral and inhaled beta$_2$ agonists; directness points deducted for use of subjective/surrogate outcome and restricting population to adults
7 (1409) [23] [36] [37] [38]	Symptom severity	Expectorants and mucolytics versus placebo	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and use of co-medication in one RCT; directness points deducted for use of subjective outcomes and agents with limited availability

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Important outcomes			Adverse effects, Complications of acute bronchitis, Quality of life, Symptom severity						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.									

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